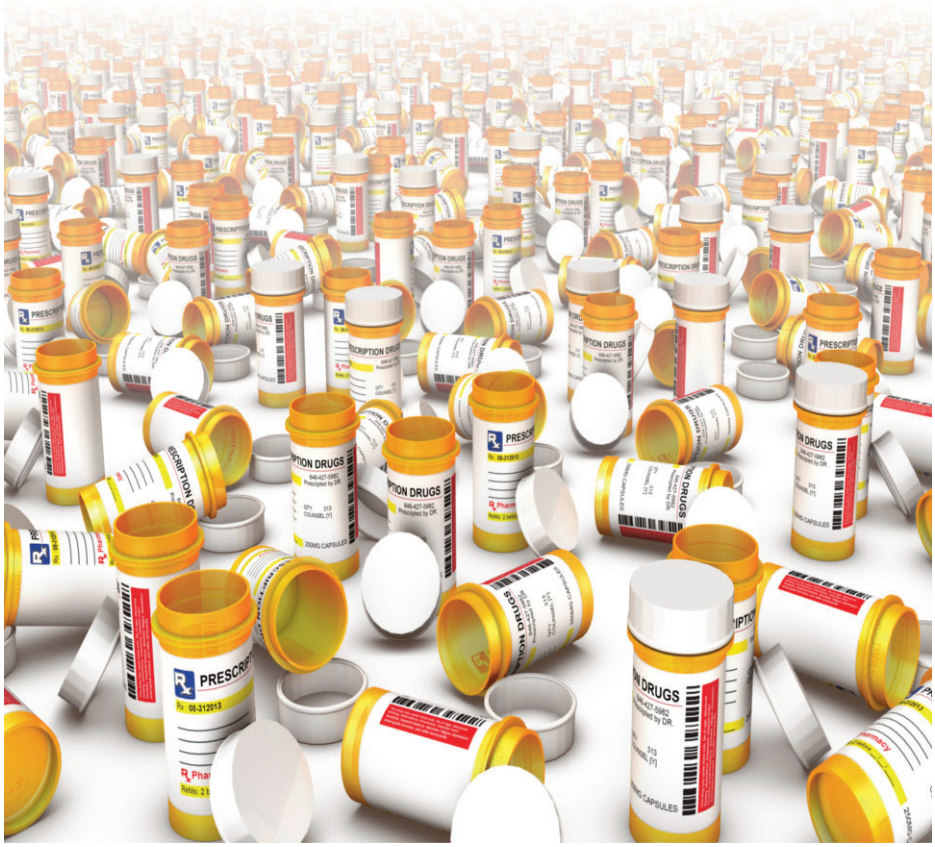
Early benefit assessment of new drugs: The impact on healthcare in Germany

Michael Köhler, Annette Christoph
Institute for Quality and Efficiency in Health Care
Cologne, Germany

Correspondence to:
Annette Christoph
Institute for Quality and Efficiency in Health Care (IQWiG)
annette.christoph@iqwig.de

Abstract

The early benefit assessment of new drugs was introduced in Germany in 2011. The main rationale was to support pricing negotiations between the statutory health insurance (SHI) system and the pharmaceutical industry. The early benefit assessment provides publicly available documents to inform healthcare decision makers at both population and individual levels. Besides drug pricing decisions by the SHI, the early benefit assessment contributes to other areas such as the development of clinical practice guidelines and shared decision making between the physician and patient. This article describes the process and content of the early benefit assessment, including details on the standardised dossier submitted by the pharmaceutical company, the dossier assessment conducted by the Institute for Quality and Efficiency in Health Care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*), and the final decision by the decision-making body, the Federal Joint Committee (*Gemeinsamer Bundesausschuss*). A case example of a dossier assessment is also presented.



The German statutory health insurance (SHI: *gesetzliche Krankenversicherung*) system is comprised of approximately 100 non-profit SHI funds.[1]

About 90% of the population is insured by the SHI and is entitled to appropriate healthcare as prescribed by the German healthcare legislation (Volume V of the Social Insurance Code).[2] SHI funds are required to reimburse approved treatments, such as new drugs, immediately upon market authorisation, and at the same time ensure the efficient use of resources. Before 2011, their price was set solely by the pharmaceutical industry, leading to high prices for new drugs, many of which had no added benefit over established drugs.[3] This changed with the 2011 Act on the Reform of the Market for Medicinal Products (AMNOG: *Arzneimittelmarktneuordnungsgesetz*) that introduced a mandatory assessment of drugs, entitled the "early benefit assessment".[4,5] The main rationale for the Act was to support pricing decisions and ultimately slow the increase in drug prices.

Early benefit assessment

Competent organisations

The Federal Joint Committee (G-BA: *Gemeinsamer Bundesausschuss*) is the main decision-making body in the German SHI system. It is a council comprising representatives from SHI funds, hospitals, licensed physicians, psychotherapists, and dentists.[6] Patient representatives contribute to discussions but do not have voting rights. The G-BA is responsible for the overall

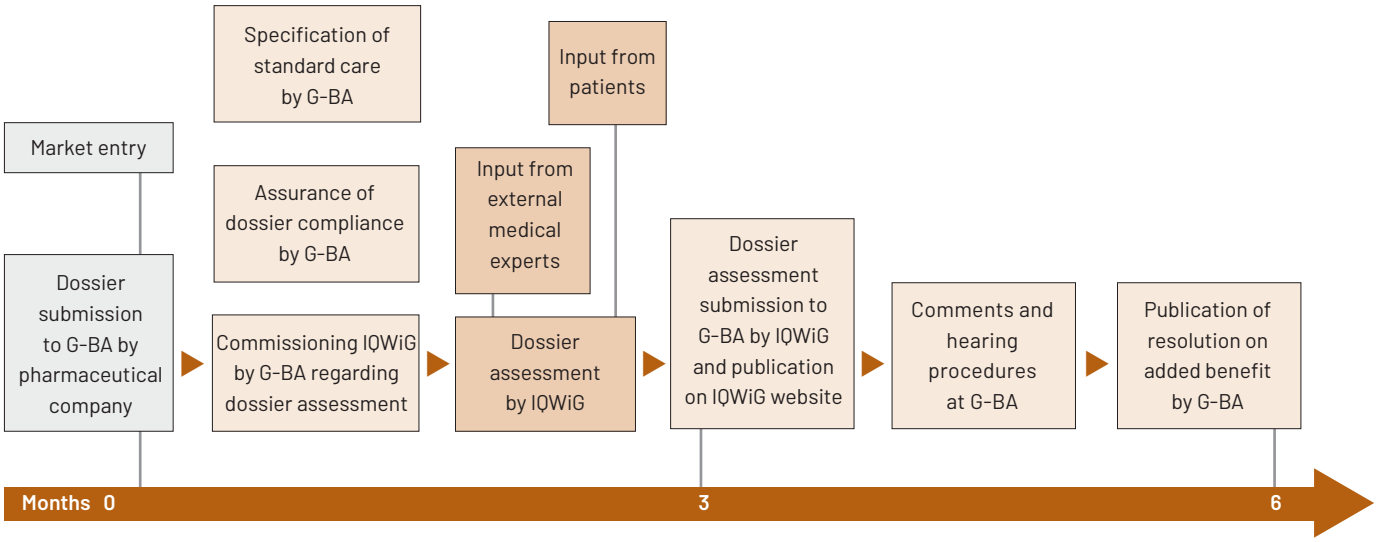


Figure 1. Stages in developing the early benefit assessment

Abbreviations: G-BA, Federal Joint Committee; IQWiG, Institute for Quality and Efficiency in Health Care

process of the early benefit assessment and for the final decision on the added benefit of a new drug.[7] The Institute for Quality and Efficiency in Health Care (IQWiG: *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*) is a German health technology assessment agency whose main responsibility is the evaluation of drug and non-drug interventions including all new drugs (except orphan drugs). IQWiG is mostly commissioned by the G-BA.[8,9]

Process, content, and impact of the assessment

The early benefit assessment process is a sequence of measures with clearly defined content and timelines (Figure 1).

When a new drug or an established drug with a new therapeutic indication enters the German market, the responsible pharmaceutical company must submit a standardised dossier to the G-BA containing all of the available evidence from clinical studies (preferably randomised controlled trials, RCTs). The G-BA makes sure that the dossier fulfils formal requirements. The dossier's scope and content are specified in a mandatory (German-language) template available on the G-BA website[3, 10] and consists of Modules 1 to 5 (see Figure 2). Modules 1-4 contain information on the new drug, the standard care (which is called the "appropriate comparator therapy" and specified by the G-BA), the number of patients affected, and costs of treatment. They also contain a systematic review that must show the new drug's added benefit over standard care. Module 5 contains the corresponding clinical study reports, parts of the submission dossier for marketing authorisation, and further information.

> The G-BA is responsible for the overall process of the early benefit assessment and for the final decision on the added benefit of a new drug.

The G-BA commissions IQWiG to assess the evidence contained in the dossier within three months after market entry; the corresponding report is called a dossier assessment (Figure 1). Before the assessment begins, external experts and patient representatives are asked to answer questionnaires relating to the drug of interest and the corresponding therapeutic indication(s). In addition, external experts provide advice on specific issues arising during the assessment.

The assessment focuses on patient-relevant outcomes such as mortality, morbidity (including adverse events), and health-related quality of life.[11] IQWiG conducts a systematic review based on the approved therapeutic indication and patient population according to the summary of product characteristics, the standard care specified, and the analysis of data on patient-relevant outcomes presented in the modules of the dossier (Fig. 2). The added benefit is determined by comparing the benefits and harms of the new drug with those of the standard care. The dossier assessment contains IQWiG's conclusions on whether the new drug has an added benefit. The following information is provided:

1. The degree of certainty of the conclusions (from low to high: hint, indication, proof of added benefit), which is determined by the amount and quality of the study data, and
2. The extent of any added benefit (minor, considerable, major, not quantifiable), which depends on the type of outcome and the effect sizes.[11] This is then resubmitted to the G-BA.

Post-assessment publications and the G-BA's final decision

The assessment process at IQWiG and the G-BA produces a number of publicly available documents (see Fig. 2). Firstly, the dossier: Modules 1-4 are published on the G-BA website. Module 5 is not published as a whole, but IQWiG may publish data in the dossier assessments as required. Secondly, the dossier assessment: The full dossier assessment is published on the IQWiG and G-BA websites 3 months after the

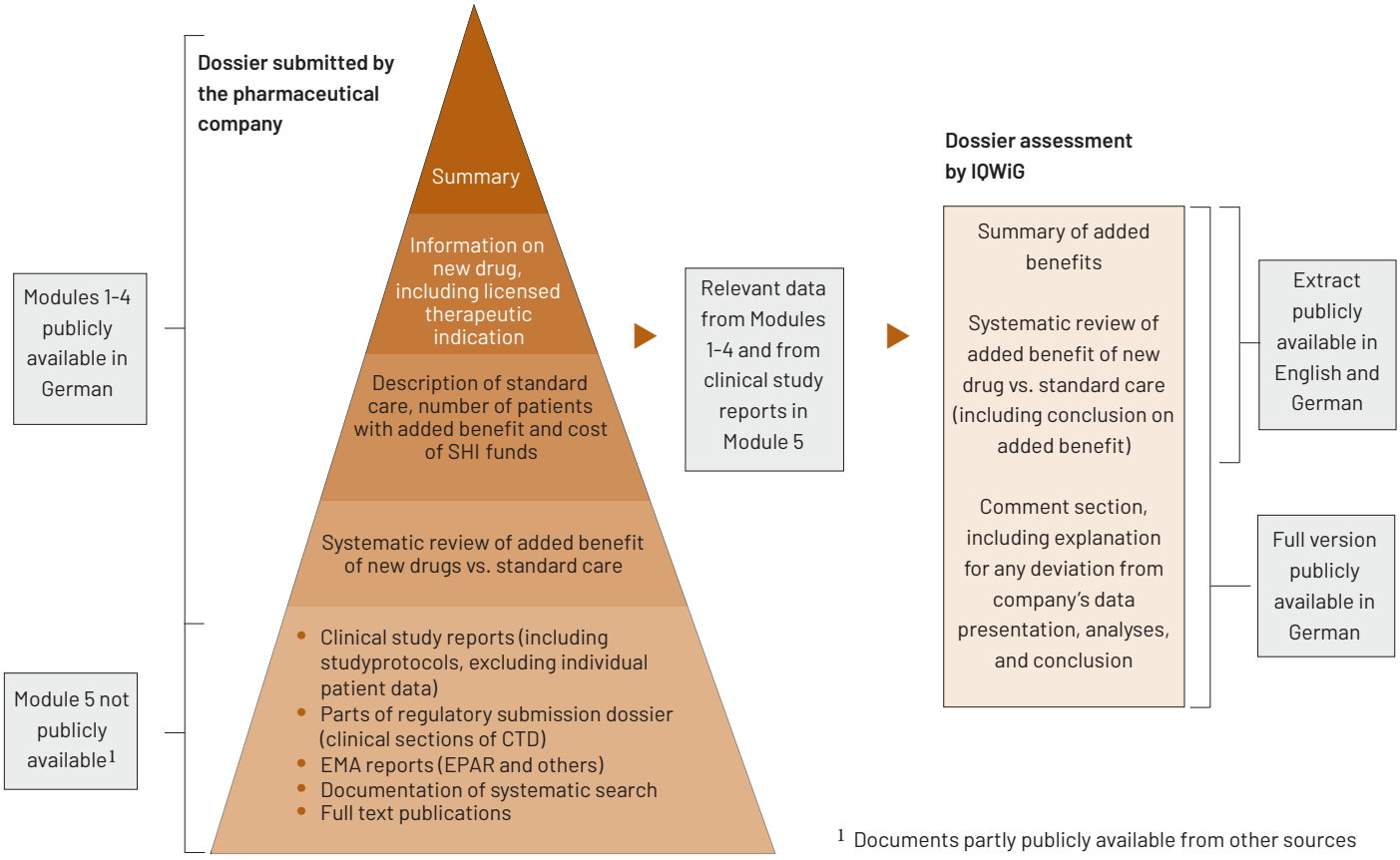


Figure 2. Structure and content of the pharmaceutical company's dossier and IQWiG's dossier assessment (modified based on Köhler et al.2015)[3]

Abbreviations: CTD, common technical document; EPAR, European public assessment report; IQWiG, Institute for Quality and Efficiency in Health Care; SHI, statutory health insurance

assessment was commissioned (Fig.1) (as an example, please see the dossier assessment on apalutamide[12]).

Thirdly, the final decision of the G-BA: This is based on the results of the dossier assessment. The dossier assessment still undergoes commenting and hearing procedures at the G-BA. Within 6 months after the drug's market entry, the G-BA publishes the final decision and a document containing the underlying reasons (*"Tragende Gründe"*) for its decision and the comments of the involved stakeholders. These documents contain clinical data from the dossier and the clinical study reports on the studies included in the dossier assessment (as an example, please see the documents on apalutamide).[13,14]

Post-assessment impact on different decision levels in healthcare

As intended by law or as an add-on, the G-BA's decision on the added benefit supports various decisions in the healthcare system at both population and individual levels. The decision ultimately addresses three main stakeholder groups with different roles and needs: payers, physicians, and patients (Fig. 3).

Payers are mainly SHI funds and, to a lesser extent, private health insurance funds (as prices negotiated by the SHI umbrella organisation are also used within the private health insurance system). All new drugs are reimbursed by the SHI, but the actual reimbursement prices are subject to negotiations based on the added benefit and are determined in the final step of the early benefit assessment. Negotiations are held between the SHI umbrella organisation and the pharmaceutical company to determine the final price.[7] No documentation on the price negotiation process is made publicly available; only the final price is published.

The conclusions on added benefit and the provision of the underlying data from the assessment process represent an additional, publicly available source of information for physicians, who can access all public AMNOG-related documents. However, searching for and screening them can be time-consuming. To facilitate access to assessment results and to promote their use in routine care, an electronic doctor information system was launched in 2020; this system is integrated into the standard prescription software. The G-BA transfers the structured files on new drugs to the software providers who make sure that physicians can access the information swiftly.[15] This tool is not meant to provide legal directives for prescribers but merely to report the evidence.

Assessment results can also be used in the development of clinical practice guidelines. Guideline developers traditionally rely on bibliographic databases as these are often the only publicly available sources of clinical study data. However, clinical study data are still not routinely available; even journal publications do not contain a full account of a clinical study.[3] The situation has begun to change for newer drugs

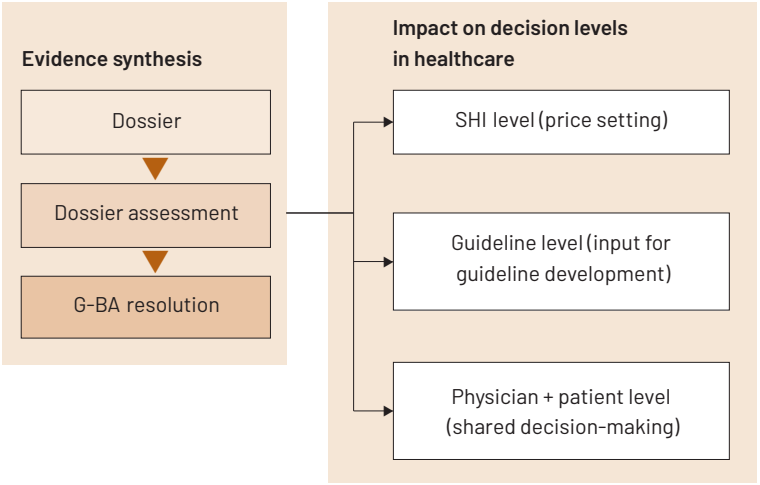


Figure 3. Impact of the early benefit assessment

Abbreviations: G-BA, Federal Joint Committee; SHI, statutory health insurance

such as through the introduced AMNOG policies and other regulatory policies, e.g. the EMA database on clinical data for marketing authorisation processes (clinicaldata.ema. europa.eu).[16, 17] Still, there are some restrictions in the EMA database that do not apply to IQWiG. Because IQWiG has access to the full clinical study reports of all relevant studies and is free to use these data in its assessments, it adds another level of valuable information for guideline developers. This important information does not only deal with the main study results but also study methods, risk of bias and other possible study limitations, as well as additional study results (including subgroup analyses).

Treatment decisions should ideally be made as shared decision-making between physicians and patients. It is therefore necessary to publish the findings from dossier assessments in an easily understandable format. This is in line with IQWiG's legal remit to provide health information on diseases of major epidemiological importance, diagnostic procedures, and treatments.[18] This type of information, including the results of all dossier assessments, is published on the IQWiG health information website *gesundheitsinformation.de* (English version: informedhealth.org).

Conclusion

The process of early benefit assessment in Germany provides publicly available, comprehensive information – in both scientific and easily understandable formats – on the added benefit of new drugs. The assessment often includes previously unpublished data. Besides informing pricing decisions, further goals are to contribute to the development of clinical practice guidelines and to shared decision-making by physicians and patients.

Acknowledgements

The authors thank Beate Wieseler and Natalie McGauran for reviewing and editing the manuscript.

Conflicts of interest

The authors are employed by the Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, Germany.

References

1. GKV-Spitzenverband. Statutory health insurance – Solidarity in action; Annual Report 2018. 2018 [cited 2021 May 07]. Available from: https://www.gkv-spitzenverband.de/media/dokumente/service_1/publikationen/geschaeftsberichte/GKV_GB2018_english_barrierefrei_01a.pdf.
2. Bundesministerium der Justiz und für Verbraucherschutz. Sozialgesetzbuch (SGB) Fünftes Buch (V) - Gesetzliche Krankenversicherung – (Artikel 1 des

The case of *apalutamide*: An example

Apalutamide is an antiandrogen used in the treatment of castration-resistant prostate cancer with a high risk of metastasis; its early benefit assessment was published in 2020.[12–14] The G-BA defined watchful waiting as standard care (while maintaining ongoing conventional androgen deprivation therapy in both study groups). The pharmaceutical company identified only one relevant randomised controlled trial (RCT), a finding that IQWiG confirmed. The patient-relevant outcomes investigated included overall survival, symptom progression, health status, health-related quality of life, and adverse events. Apalutamide showed more favourable effects, especially on overall survival, serious or severe symptoms, and some adverse events. For other adverse events, standard care showed more favourable effects. Since apalutamide showed an added benefit for overall survival, the unfavourable effects did not offset the favourable ones. IQWiG thus concluded that the data provided an indication of a considerable added benefit of apalutamide.

Gesetzes v. 20. Dezember 1988, BGBl. I S. 2477); § 12 Wirtschaftlichkeitsgebot. [cited 2021 May 18]. Available from: https://www.gesetze-im-internet.de/sgb_5/__12.html.
3. Köhler M, Haag S, Biester K, Brockhaus AC, McGauran N, Grouven U, et al. Information on new drugs at market entry: retrospective analysis of health technology assessment reports versus regulatory reports, journal publications, and registry reports. BMJ. 2015;350:h796.
4. Bundesministerium für Gesundheit. Gesetz zur Neuordnung des Arzneimittelmarktes in der gesetzlichen Krankenversicherung (Arzneimittelmarktneuordnungsgesetz - AMNOG). Bundesgesetzblatt. 2010(67):2262–77.
5. Horn H, Nink K, McGauran N, Wieseler B. Early benefit assessment of new drugs in Germany – results from 2011 to 2012. Health Policy. 2014;116(2-3):147-53.
6. Gemeinsamer Bundesausschuss. The Federal Joint Committee: Who we are and what we do [cited 2021 May 14]. Available from: https://www.g-ba.de/english/structure/.
7. Gemeinsamer Bundesausschuss. The benefit assessment of medicinal products in accordance with the German Social Code, Book Five (SGB V), section 35a. [cited 2021 May 07]. Available from: https://www.g-ba.de/english/benefitassessment/.
8. Institute for Quality and Efficiency in Health Care. Responsibilities and objectives of IQWiG [cited 2021 May 14]. Available from: https://www.iqwig.de/en/about-us/ responsibilities-and-objectives-of-iqwig/.
9. Institute for Quality and Efficiency in Health Care. Contracting agencies and funding of IQWiG. [cited 2021 May 14]. Available from: https://www.iqwig.de/en/about-us/responsibilities-and-objectives-of-iqwig/contracting-agencies-and-funding/.
10. Gemeinsamer Bundesausschuss. Anlage II zum 5. Kapitel – Format und Gliederung des Dossiers, einzureichende Unterlagen, Vorgaben für technische Standards. 2021 [cited 2021 May 07]. Available from: https://www.g-ba.de/richtlinien/anlage/167/.
11. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0. 2020 [cited 2021 May 18]. Available from: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.
12. Institute for Quality and Efficiency in Health Care. Apalutamide (prostate cancer) – Benefit assessment according to §35a Social Code Book V (expiry of the decision); Extract. 2020 [cited 2021 May 07]. Available from: https://www.iqwig.de/download/a20-36_apalutamide_ extract-of-dossier-assessment_v1-0.pdf.
13. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Apalutamid (Neubewertung nach Fristablauf: nicht-metastasiertes, kastrationsresistentes Prostatakarzinom). 2020 [cited 2021 May 07]. Available from: https://www.g-ba.de/downloads/39-261-4483/2020-10-01_AM-RL-XII_Apalutamid_D-538_BAnz.pdf.
14. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Apalutamid (Neubewertung nach Fristablauf: nicht-metastasiertes, kastrationsresistentes Prostatakarzinom). 2020 [cited 2021 May 07]. Available from: https://www.g-ba.de/downloads/40-268-6910/2020-10-01_AM-RL-XII_Apalutamid_D-538_TrG.pdf.
15. Bundesministerium der Justiz und für Verbraucherschutz. Verordnung über die Mindestanforderungen an die Informationen in elektronischen Programmen für die Verordnung von Arzneimitteln durch Vertragsärzte und über die Veröffentlichung der Beschlüsse des Gemeinsamen Bundesausschusses (Elektronische Arzneimittelinformationen-Verordnung – EAMIV). 2019 [cited 2021 May 03]. Available from: https://www.gesetze-im-internet.de/ eamiv/BJNR111000019.html.
16. European Medicines Agency. Publication of clinical reports. 2014 [cited 2021 May 14]. Available from: https://www.ema.europa.eu/en/news/publication-clinical-reports.
17. Agency EM. European Medicines Agency - Clinical Data [cited 2021 June 02]. Available from: https://clinicaldata.ema.europa.eu/ web/ cdp/home.
18. Bundesministerium der Justiz und für Verbraucherschutz. Sozialgesetzbuch (SGB) Fünftes Buch (V) – Gesetzliche Krankenversicherung – (Artikel 1 des Gesetzes v. 20. Dezember 1988, BGBl. I S. 2477); § 139a Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [cited 2021 May 07]. Available from: https://www.gesetze-im-internet.de/sgb_5/__139a.html.

Author information

Michael Köhler was previously a medical writer at a contract research organisation and is currently a Research Associate in the Drug Assessment Department at the Institute for Quality and Efficiency in Health Care (IQWiG).

Annette Christoph was previously an Associate Principal Clinical Scientist with a pharmaceutical company (Grünenthal GmbH) and is currently a Research Associate in the Drug Assessment Department at IQWiG.